Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 89-102, 116 and 123-129 under the judicially created doctrine of obviousness-type double patenting over claims 1-95 of US patent 5,750,497.

In response, Applicants submit that this rejection is rendered moot by the terminal disclaimer submitted herewith. Applicants note that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting and raises neither a presumption nor estoppel on the merits of the rejection". Quad Environmental Technologies Corp. v. Union Sanitary District, 20 USPQ 2d 1392 (Fed. Cir. 1991).

Rejection Under 35 USC § 103(a)

Claims 89-102, 116, and 123-139 were rejected as obvious over Ganong (Review of Medical Physiology, pp 280-282, 1989) in view of Lindsay et al. (US 3,950,517), Markussen (US 5,008,241) and Gammeltoft (1984) Phys. Rev. 6494): 1321-1378.

In setting forth the above rejection[1], the Examiner states:

> One of ordinary skill in the art would have been motivated to modify Ganong et al insulin by Lindsay et al's acylation in order to make the insulin more physiological acceptable. It would have been prima facie obvious to apply Lindsay et al's modification to Ganong et al's insulin in order to reduce the antigenicity, thereby reducing the individual's immunoreactivity to the pharmaceutical insulin while still maintaining its physiological function (see col.3 line 10-25).
>
> Moreover, one of ordinary skill in the art at the time of the invention was made would have been motivated to further modify Ganong's insulin by the teachings of Markussen, Gammeltoft, and Marunishi in order to increase the stability, solubility and prolonged activity. It would have been prima facie obvious to apply of Markussen, Gammeltoft and Marunishi modifications to increase the stability of Ganong's insulin for pharmaceutical injections (page 5 of Office Action).

Applicants respectfully traverse this rejection.

[1] Even assuming arguendo that the Examiner has established a prima facie case of obviousness for claims where B1 is Phe, Applicants submit that claims 92 and 93, where B1 is deleted, are nonobvious over the cited art because the only reference cited by the Examiner as teaching B1 as a residue other than Phe is Gammeltoft but Gammeltoft merely teaches the substitution of B1 Phe with iodo or diiodo-tyrosine (see page 1327 of Gammeltoft), and not the deletion of the B1 Phe residue as recited in claims 92 and 93.

"To establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was claimed" [In re Kotzab, 554 USPQ2d 1308, 1316 (Fed. Cir. 2000), emphasis added]. Of course, it is well settled that the prior art references must be viewed without the benefit of hindsight afforded by the inventor's disclosure. In re Paulsen 31 USPQ 2d 1671,1674 (Fed. Cir.1994). Moreover, a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. W.L.Gore & Associates Inc. v. Garlock Inc., 220 USPQ 303 (Fed. Cir. 1983) cert denied, 469 U.S. 851 (1984).

In the present Office Action, the Examiner asserts that "it would have been prima facie obvious to apply Lindsay's et al's modification to Ganong et al's insulin in order to reduce the antigenicity" (see page 5 of Office Action). According to the Examiner, " Lindsay et al's modification" is the acylation of the epsilon amino group of B29 Lys where the acyl group may have up to 7 carbon atoms (see page 4 of Office Action).

However, Applicants submit that a proper reading of Lindsay in its entirety reveals that Lindsay teaches that 1) the acyl group attached to B29 Lys is 4 carbons or less and 2) derivitization at the B29 position produces a reduction in immunoreactivity with insulin antibodies that is weaker and less desirable than that of the other derivatives tested by Lindsay.

With respect to the first point, Lindsay describe insulin derivatives where B1 Phe is protected by an acyl group containing up to 7 carbon atoms and the A1 Gly is free or protected by an acyl group containing no more than four carbon atoms and preferably no more than 3 carbon atoms. (see Abstract and col. 1, lines 24-34).

The specification of Lindsay further discloses that acylation of B29 Lys can be used to achieve trisubstituted derivatives (col. 2, lines 2-4) and that monosubstitution at A1 Gly, B1 Phe and B29 Lys can occur (see col. 2, lines 59-61 and Table 1). However, the Lindsay patent makes it explicitly clear that the acyl group attached to the B29 Lys, like the acyl group attached to the A1 Gly, is to be no greater than 4 carbon atoms in length. For example, claim 1 is directed to a pharmaceutical composition comprising a mono-, di- or trisubstituted insulin where the amino group of B29 Lys is "either free or protected by an acyl or other substituent containing no more than 4 carbon atoms"). Thus, contrary to the Examiner's assertion, Lindsay does not teach acylation of B29 Lys with an acyl group of up to 7 carbon

atoms. Indeed, Lindsay explicitly discloses that the acyl group attached to B29 Lys should not be greater than 4 carbon atoms.

Turning to the second point, Lindsay discloses a method for protecting porcine and bovine insulin from reacting with specific insulin antibodies by acylating free amino groups of the insulin molecule. In discussing its acylated insulin derivatives and the results shown in Tables 1 and 2, Lindsay states: "the derivatives have less than about 50% of the immunoreactivity of the parent insulin as determined by radioimmunoassay." (Col.3, lines17-19). However, reference to Tables 1 and 2 reveals that the only monosubstituted insulins having the desired reduction in immunoreactivity are those substituted at the B1 Phe residue. By comparison, the two monosubstituted B29 Lys derivatives only show reductions in immunoreactivity relative to the parent insulin of 17 and 16% respectively. These reductions are far less than those observed for the di- and tri-substituted insulins and for the insulins monosubstituted at B1 Phe and far less than the aforementioned 50% or greater reduction in immunoreactivity desired by Lindsay. Clearly, even assuming arguendo that one would have been motivated to acylate the insulin of Ganong in order to reduce its immunoreactivity with insulin antibodies, one of ordinary skill in the art reading Lindsay in its entirety without the benefit of improper hindsight afforded by the present application would have been motivated to select the aforementioned di- and tri- substituted insulins or B1 Phe monosubstituted insulins over the B29 Lys monosubstituted insulin.

Accordingly, in view of the above arguments, it is Applicants' position that, contrary to the Examiner's assertion, one would not have been motivated by Lindsay to modify Ganong's insulin by acylation at the B29 position with an acyl group of up to seven carbon atoms in order to reduce its immunoreactivity with insulin antibodies.

It is also Applicants' position that the Examiner, in rejecting the above claims, has improperly used hindsight analysis in selectively picking and choosing modifications from each reference to produce the specific combination of modifications recited in the claims.

Here, independent claim 89 is directed to insulin derivatives having specific modifications to the primary amino acid sequence of native insulin; namely, insulin derivatives wherein:

(a) Xaa at positions A21 and B3 are, independently, any amino acid residue, which can be coded for by the genetic code except Lys, Arg and Cys;

(b) Xaa at position B1 is Phe or is deleted;

(c) Xaa at position B30 is deleted; and

(d) the ε-amino group of Lys^{B29} is substituted with a lipophilic substituent having at least 6 carbon atoms.

Support for Applicants' position that the Examiner has improperly used hindsight analysis in selectively picking only certain modifications from each reference is provided by reference to the Examiner's reliance on Markussen and Gammeltoft.

Markussen is cited by the Examiner as providing the modification of the A21 residue recited in the claims because Markussen teaches substitution of different amino acids for the A21 Asn in order to improve the stability of the insulin at acidic pH levels. However, while the claims recite that the amino acid at A21 may be any amino acid except Lys, Arg and Cys, Markussen specifically teaches that a set of preferred substituents at the A21 position are Lys and Arg (col. 3, lines 23-24 of Markussen).

Gammeltoft is cited by the Examiner as providing the deletion of the B30 residue recited in the claims because Gammeltoft teaches that amino acids B28-B30 are not required for activity. However, the question raised by the teachings of Gammeltoft is why one skilled in the art would choose to delete only residue B30 as opposed to residues B28-B30 (or B29-B30) especially when, as discussed above, Lindsay teaches that a much greater reduction in immunoreactivity to insulin antibodies is achieved by monoacylation at B1 Phe then by monoacylation at B29 Lys.

Moreover, the teachings of Markussen as a whole would appear to be in conflict[2] with the Examiner's reliance on Gammeltoft for the deletion of B30 recited in the claims. Specifically, Markussen discloses that in its A21-substituted analogs, "preferably" the carboxylic acid group of the B30 amino acid is blocked by an amide or ester residue. (see col. 3, lines 3-5). Thus, the question is raised as to why one skilled in the art seeking to improve the solubility of one's insulin analog (ie the motivation relied on by the Examiner for including the A21 substitutions of Markussen in the insulin of Ganong) would delete the

[2] Applicants also note that the teaching of Markussen relied on by the Examiner (substitution of different amino acids for the A21 Asn in order to improve the stability of the insulin at acidic pH levels) as part of the §103 rejection of claims 89-102, 116 and 123-139 actually teaches away from the insulin derivatives of claims 100, 101, 125 and 136, where the A21 Asn is left unmodified. Simply put, Applicants submit that it is inconsistent for the Examiner to rely on Markussen to reject claims where A21 is an amino acid other than Asn (eg claim 89) and to also rely on Markussen to reject claims where the Asn at A21 is left unmodified

"functionally unimportant" B30 residue rather than retaining the B30 residue and modifying it as "preferably" taught by Markussen. The clear answer to the above question is that there is no reason to selectively delete the B30 residue other than the impermissible use of hindsight by the Examiner.

Accordingly, in view of the above remarks, it is respectfully submitted that the Examiner has failed to establish a prima facie case of obviousness and withdrawal of the §103 rejection is therefore respectfully requested.

Early and favorable action by the Examiner is respectfully requested.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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